PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 473/00 — A1

(11) International Publication Number: WO 97/18211

(43) International Publication Date: 22 May 1997 (22.05.97)

(21) International Application Number: PCT/EP96/04882

(22) International Filing Date: 6 November 1996 (06.11.96)

(30) Priority Data:
MI95A002333 14 November 1995 (14.11.95) IT

(71) Applicant *(for all designated States except US)*: ARCHIMICA S.P.A. [IT/IT]; Viale Europa, 11, I-21040 Origgio (IT).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: BELLANI, Piero [IT/IT]; Via Trento, 10, I-20017 Rho (IT).

(74) Agents: DRAGOTTI, Gianfranco; Saic Brevetti S.r.l., Galleria San Babila, 4/D, I-20122 Milano (IT) et al.

(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

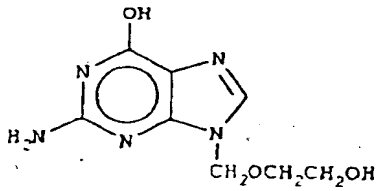
(54) Title: PROCESS FOR THE PREPARATION OF 9-[(2-HYDROXYETHOXY)METHYL]GUANINE

(57) Abstract

There is described a process for the preparation of acyclovir by hydrolysis of N^2-acetyl-9-(2-acetoxyethoxymethyl)guanine with monoethanolamine and isolation of acyclovir by neutralization with an acid and filtration. There is furthermore described a method for the purification of acyclovir by transformation of it into one of its alkali metal salts and neutralization of the alkali metal salt thus obtained.

PROCESS FOR THE PREPARATION OF 9-[(2-HYDROXYETHOXY)METHYL]GUANINE

The present invention relates to a process for the preparation of 9-[(2-hydroxyethoxy)methyl] guanine, known under its International Non-proprietary Name "acyclovir", hereinbelow designated by this name and represented by the following structural formula I



(I)

Acyclovir has been disclosed for the first time in Belgian patent 833,006; in this document there are also described various processes for its preparation, including the process involving the final step of transformation of the O-protected acyclovir into acyclovir. The expression "O-protected acyclovir" designates the protected acyclovir on the aliphatic hydroxy group. According to this method, the O-protecting group is, in general, an ester, more particularly an acyl group, preferably a benzoyl group. Removal of the O-protecting group is carried out, according to BE 833,006, by treatment with ammonia saturated methanol to give acyclovir in a 75% yield.

Other methods for the preparation of acyclovir are indicated by the literature. Thus, EP 532,878 discloses the preparation of O,N^2-diprotected acyclovir by acetylation and subsequent deprotection by treatment with sodium hydroxyde to give acyclovir in a 92% yield. According to this document, however, diacetylacyclovir [N^2-acetyl-9-(2-acetoxyethoxymethyl)guanine] is in its turn obtained in admixture with N^2-acetyl-7-(2-acetoxyethoxymethyl)guanine in the 2.5:1 ratio which requires a previous chromatographic separation of the two isomers.

An analogous synthesis is described by H. Matsumoto et al. in Chem. Pharm. Bull. 1988, 36, 1153, where, after the separation of the two acetylated isomers, the hydrolysis of diacetylacyclovir is carried out with agueous ammonia to give acyclovir in a 55% yield.

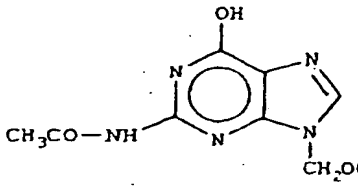
In EP 564,006, the preparation of 9-(2-acetoxyethoxymethyl)guanine and N^2-acetyl-9-(2-acetoxyethoxymethyl)guanine is described. The conversion into acyclovir is carried out with a basis, particularly

with ammonia, a 50% aqueous solution of methylamine, sodium methylate or sodium hydroxide even though it is not exemplified.

The document IT MI 93A001264 discloses a process for obtaining acyclovir which is substantially analogous to that described in BE 833,006, whereby O-protected acyclovir is used as starting material, the protecting group being acyl and the deprotection being carried out with sodium hydroxide.

The above mentioned documents and in general the known methods for the preparation of acyclovir involve, at the end of the synthesis, complex purifications, more particularly a passage of very diluted aqueous solutions of the product on columns of ionic resins, which render such methods somewhat laborious.

It has now been found that acyclovir in a pharmacologically acceptable purity state can be prepared in very high yields by hydrolysis of diacetylacyclovir of formyla II

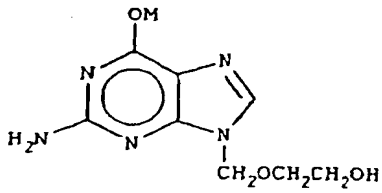


(II)

by hydrolysis with an aqueous solution of an alcanolamine, preferably monoethanolamine.

It has also surprisingly found that, by hydrolysis with aqueous monoethanolamine, acyclovir precipitates straightforward in the reaction medium and may be thus isolated by simple filtration in a purity state at least sufficient to be pharmacologically acceptable.

Finally, it has been found that acyclovir may be easily purified by transformation in one of its alkali metal salts of formula III



(III)

wherein M is an atom of an alkali metal, preferably sodium or potassium, and subsequent neutralization of the aqueous solution of

said salt.

Thus, according to one of its aspects, the present invention concerns a process for the preparation of acyclovir which comprises

(a) treating the N^2-acetyl-9-(2-acetoxyethoxymethyl)guanine (diacetylacyclovir) with an alcanolamine in aqueous solution;

(b) isolating the acyclovir thus obtained by treatment with a mineral or organic acid and subsequently filtering the separated precipitate.

In the preferred realization form, step (a) is carried out with monoethanolamine.

Step (a) is carried out starting from a N^2-acetyl-9-(2-acetoxy ethoxymethyl)guanine which may be pure or in a wet state by the residual solvent of its synthesis, in aqueous medium at a temperature of 70÷95°C. At this temperature the reaction is complete after about 3 hours.

Among the alcanolamines, monoethanolamine is preferred but appreciable results are obtained also using diethanolamine and triethanolamine, even though with longer reaction times.

In step (b), after the possible removal of the residual solvent, for example by distillation under vacuum, the reaction mixture is treated with an acid, for example with acetic acid, up to neutrality. Acyclovir thus obtained is isolated by filtration and subsequent washing with an appropriate solvent, for example a ketone such as acetone, methylethylketone or methylisobutylketone, and final drying.

In general, the product obtained is of great purity, read for use in pharmaceutical formulations.

If a further increase of the purity degree or if an acyclovir obtained by another route is available, the product may be, in general, purified by transformation in one of its alkali metal salts, preferably in its sodium salt and subsequent neutralization in aqueous medium. Such a purification presents the advantage that it can be carried out on any crude acyclovir obtained according to any other method.

According to another of its aspects, the present invention provides a method for the purification of acyclovir which comprises

(c) treating acyclovir with an alkaline basis; and

(d) neutralizing the thus isolated salt by addition of an acid in aqueous medium and isolating the pure acyclovir thus obtained by filtration.

In step (c) the crude acyclovir, for example the product obtained at the end of the above illustrated step (b), even if it is wet by washing solvent, is treated with an alkaline basis, for example with sodium or potassium hydroxide or with sodium or potassium carbonate, in aqueous medium and an organic solvent, preferably a ketone such as acetone, methylethylketone or methylisobutylketone is added to the clear solution; preferably this solvent is the same which has been used for washing acyclovir, when this product has been prepared according to the above illustrated steps (a) and (b).

The acyclovir alkali metal salt thus obtained is isolated by precipitation according to conventional methods, by decolorizing with carbon, if needed, the solution of the salt before the precipitation, then filtering the product and washing it. It is employed as such in the subsequent step.

In step (d) the alkali metal salt thus obtained is neutralized in aqueous medium with a mineral or organic acid, for example with hydrochloric or hydrobromic, acetic, propionic or methanesulfonic acid and the acyclovir in a high purity degree thus obtained is isolated by filtration, subsequent washing and drying.

According to a preferred aspect, the present invention finally concerns a process for the preparation of highly pure (≥ 99%) 9-(2-hydroxyethoxymethyl)guanine which comprises

(a) treating N^2-acetyl-9-(2-acetoxyethoxymethyl)guanine of formula II with monoethanolamine in aqueous medium;

(b) isolating the 9-(2-hydroxyethoxymethyl)guanine thus obtained by neutralization with acetic acid and filtration of the separated precipitate;

(c) treating the wet 9-(2-hydroxyethoxymethyl)guanine with sodium hydroxide in aqueous medium and letting the sodium salt to precipitate, which is isolated by filtration;

(d) neutralizing the wet sodium salt thus obtained with acetic acid

in aqueous medium and isolating the thus obtained very pure 9-(2-hydroxyethoxymethyl)guanine by filtration.

The process of the present invention, on one side, allows the preparation of acyclovir by a method which gives it straightforward in a pure crystalline state at the end of the deprotection reaction of the diacetylacyclovir and, on the other side, allows a further purification of acyclovir without using particular apparatus, expecially ionic resins columns.

The following examples illustrate the invention without, however, limiting it.

EXAMPLE 1

A mixture of 46.250 g (0.149 moles) of N^2-acetyl-9-(2-acetoxyethoxy methyl)guanine and 32.750 g (0.536 moles) of monoethanolamine in 600 ml of deionized water are heated at 90°C for 3 hours under stirring, then it is cooled to 60°C and 25 ml of 80% acetic acid are added thereinto to reach a pH of 6.8÷7.2. The mixture is further cooled to about 20°C, then 60 ml of water and 60 ml of acetone are added thereinto. The crystalline product is filtered and washed with acetone. Thus, there is obtained 50 g of acyclovir, wet of acetone, corresponding to 33.250 g of an acyclovir having purity characteristics corresponding to those of a USP standard. Yield: 98.7% of the theoretical.

EXAMPLE 2

(a) To a mixture of 30 g of acyclovir, wet of acetone, obtained according to Example 1 and corresponding to 19.950 g of dry product, 36 ml of deionized water and 9 ml of 30% sodium hydroxide are added in order to have a pH of 11.8 ÷ 12.0, then 37.5 ml of acetone and 150 ml of decolorizing charcoal are added into the solution. The mixture is filtered, by washing with 1.5 ml of deionized water and 1.5 ml of acetone, the solution is heated to 35°C and 195 ml of acetone are added thereinto. The suspension thus obtained is cooled to 15°C, stirred 2 hours at the same temperature, filtered and the product is washed with 35 ml of acetone. There is obtained 25.5 g of sodium salt, wet of acetone, corresponding to 23.2 g of dry product.

(b) To a solution of 24 g of acyclovir sodium salt, wet of acetone,

as obtained according to (a) and corresponding to 21.9 g of dry product, in 220 ml of deionized water, 6.75 ml of 80% acetic acid are added. The suspension of the crystalline product thus obtained is cooled at 15°C and stirred for 1 hour. Then it is filtered, washed with 35 ml of deionized water and 35 ml of acetone, then dried under vacuum at 80°C up to a residual moisture not higher than 5%. So, there is obtained 18.2 g of acyclovir having a purity of 99.85%.

EXAMPLE 3

By operating as described in Example 1, from 17.5 g of N^2-acetyl-9-(2-acetoxyethoxymethyl)guanine 18.9 g of acyclovir, wet of acetone, are obtained. By drying under vacuum at 80°C up to constant weight, 12.650 g of acyclovir with a purity of 99.25% are obtained.

EXAMPLE 4

By operating as described in Example 2, starting from 4.750 g of acyclovir with a purity of 95.47%, prepared according to Example 6 of BE 833,006, 5.08 g of sodium salt are obtained. By neutralization in aqueous solution of the sodium salt thus obtained, using 80% acetic acid, 4.220 g of acyclovir with a purity of 99.27% are obtained.

CLAIMS

1. Process for the preparation of 9-(2-hydroxyethoxymethyl)guanine which comprises

(a) treating the N^2-acetyl-9-(2-acetoxyethoxymethyl)guanine with an alcanolamine in aqueous solution;

(b) isolating the acyclovir thus obtained by treatment with a mineral or organic acid and filtering the separated precipitate.

2. A process according to claim 1, in which said alcanolamine is selected from the group consisting of mono-, di- and triethanolamine.

3. A process according to claim 2, in which said alcanolamine is monoethanolamine.

4. A process according to claim 1, in which the reaction temperature in step (a) is of 70÷95°C.

5. A process according to claim 1, in which acetic acid is employed in step (b).

6. A process for the purification of 9-(2-hydroxyethoxymethyl) guanine, which comprises

(c) treating 9-(2-hydroxyethoxymethyl)guanine with an alkaline basis; and

(d) neutralizing the thus isolated alkaline salt by addition of an acid in aqueous medium and isolating the pure 9-(2-hydroxyethoxy methyl)guanine thus obtained.

7. A process according to claim 6, in which sodium or potassium hydroxide is used as alkaline basis in step (c).

8. A process for the preparation of 9-(2-hydroxyethoxymethyl) guanine having an at least pharmacologically acceptable purity, which comprises

(a) treating N^2-acetyl-9-(2-acetoxyethoxymethyl)guanine with mono ethanolamine in aqueous medium;

(b) isolating the 9-(2-hydroxyethoxymethyl)guanine thus obtained by treatment with acetic acid and filtration of the precipitate thus obtained;

(c) treating the wet 9-(2-hydroxyethoxymethyl)guanine with sodium hydroxide; and;

(d) neutralizing the wet sodium salt thus obtained with acetic acid

in aqueous medium and isolating the thus obtained pure 9-(2-hydroxy ethoxymethyl)guanine.